

Docket No.: 2815-0347PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brian FROSTRUP et al.

Application No.: 10/566,384

Confirmation No.: 5532

Filed: January 30, 2006

Art Unit: 4161

For: 2-METHOXYMETHYL-3-(3,4-
DICHLOROPHENYL)-8-
AZABICYCLO[3.2.1]OCTANE TARTRATE
SALTS

Examiner: Valerie Rodriguez-Garcia

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Brian Frøstrup, declare the following:

I am the Head of Preformulation at NeuroSearch of Ballerup, Denmark.

A copy of my curriculum vitae is attached hereto.

I have read and understand the specification and claims to the above-identified application and the outstanding Office Action of July 10, 2008 (hereinafter "Office Action").

I have also read and considered within the Office Action the 35 U.S.C. 103(a) rejection.

As to the above rejection, the Examiner cites Scheel-Kruger *et al.*, US Patent No. 6,288,079 B1 (which is the U.S. equivalent to WO 97/30997) in which the citrate salt is mentioned.

Below is data that shows that the salt of the present invention, when compared to the citrate salt of Scheel-Kruger *et al.*, shows an unexpected substantial improvement in hygroscopic properties. The non-hygroscopic nature of the tartrate salt is important for any commercial use. Scheel-Kruger *et al.* do not teach or suggest that the tartrate salt would possess any such special properties. Based on the above, as well as the data below, the unexpected substantial improvement in hygroscopic properties of the tartrate salt is an unexpected advantageous result.

The above arguments and the data explained below were presented to the International Preliminary Examining Authority (IPEA) when replying to the First Written Opinion of the ISA. Based on the above submission, the IPEA acknowledged the inventive step of the claimed invention. Enclosed is Exhibit A, which is a copy of the positive International Preliminary Report on Patentability (IPRP), for the Examiner's convenience and consideration. The IPRP discussed the data presented below.

In support of the Response to the Office Action, the following data is presented:

Hygroscopicity as measured by Dynamic Vapour Sorption (DVS)

The citrate salt and the L-tartrate salt (monohydrate) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane were tested for their water sorption characteristics as a function of increasing and decreasing humidity.

The sample weight was taken as the dry weight after equilibration at 0%RH (relative humidity). The adsorption cycles were sequentially stepped at 10% intervals from 0% to 95%RH.

The desorption cycle was the reverse of the adsorption cycle and was sequential after the adsorption cycle. A second adsorption-desorption cycle was also sequentially performed.

Citrate salt

The DSV sorption profile for the citrate salt is shown in Figure 1. The profile shows the salt to be hygroscopic. The mass increase of up to 3% at ambient relative humidity indicates the formation of a monohydrate. At high relative humidity the mass increase is 15% or more. When decreasing the relative humidity, the salt keeps about 5 % mass increase.

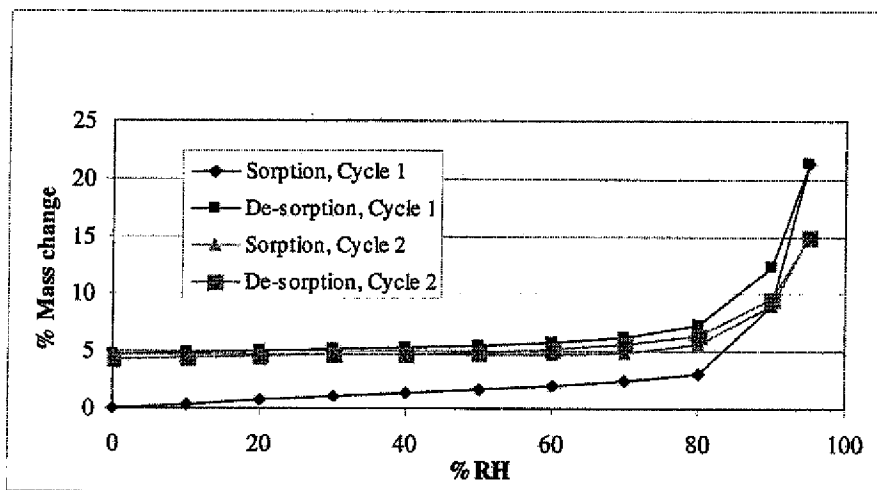


Figure 1. DSV sorption profile of the citrate salt.

Tartrate salt

The DSV sorption profile for the tartrate salt is shown in Figure 2. The profile shows the salt to be non-hygroscopic. A mass increase (up to 0.16 %) was due to adsorption on the surface of the compound.

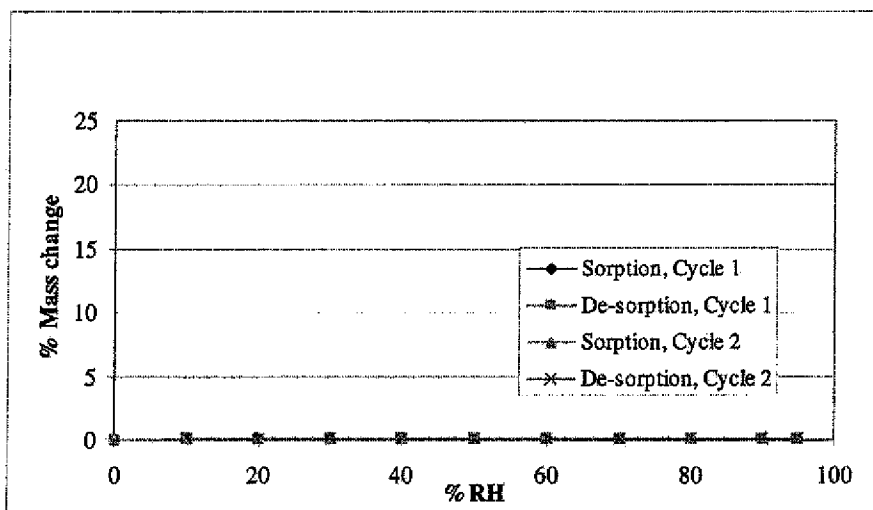


Figure 2. DSV sorption profile of the tartrate salt.

Thus, based on the above data, when compared to the citrate salt of Scheel-Kruger *et al.*, the salt of the present invention shows an unexpected substantial improvement in hygroscopic properties. As indicated in the data, the DSV sorption profile for the citrate salt (as shown in Figure 1) shows the citrate salt to be hygroscopic. The mass increase at ambient relative humidity indicates the formation of a monohydrate. When comparing the present invention to the citrate salt, for cycle 1, there is a near 20% improvement in mass change at high relative humidity. At decreasing humidity there is still a baseline improvement of 5% change in mass.

Also indicated is a near 15% improvement in mass change for cycle 2 at high relative humidity and the same baseline improvement of 5% change in mass.

As indicated, the non-hygroscopic nature of the tartrate salt is important for any commercial use. Scheel-Kruger *et al.* do not teach or suggest that the tartrate salt would possess any such special properties. The data provided shows that the unexpected substantial improvement in hygroscopic properties of the tartrate salt is an unexpected advantageous result.

STATEMENT UNDER 18 U.S.C. § 1001

I hereby declare that all statements made herein of any own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 2008-11-05

Brian Frøstrup
Brian Frøstrup

Enclosures: Exhibit A: International Preliminary Report on Patentability

NEUROSEARCH

BFR
05.11.2008

CURRICULUM VITAE

Name:	Brian Frøstrup
Born:	December 16, 1973
Graduated:	July 1999, Royal Danish School of Pharmacy
Diploma Brewmaster	March 2001, Scandinavian School of Brewing
September 1999 - March 2001	Brewmaster Trainee, Carlsberg Copenhagen
April 2001 - May 2001	Brewmaster , Carlsberg Copenhagen
June 2001 - February 2004	NeuroSearch, Research scientist, Pharmaceutical development Major field of work: Solid and solution state characterization of new chemical entities.
March 2004 -	NeuroSearch, Head of Preformulation. Major field of work: Solid and solution state characterization of new chemical entities.

Publications

Poster

Frøstrup, B., Jensen, K.S, Solid-state characterisation of *NSB L-Tartrate* Monohydrate and Anhydrous Form II and Form III. PhandTA 7. Sep 2003.

Patent publications

WO 2005/011694, filed on 29-07-2004

2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate salts
Brian Frøstrup, Frank Wätjen, Klaus Snej Jensen

WO 2006/064031, filed on 15-12-2005

Enantiomers of 3-heteroaryl-8H-8-azabicyclo (3.2.1)oct-2-ene and their use as monoamine neurotransmitter re-uptake inhibitors

Dan Peters, David Tristram Brown, Börje Egestad, Eva Dam Christoffersen, David Spencer Jones, Brian Frøstrup, Elsebet Østergaard Nielsen, Gunnar M. Olsen, John Paul Redrobe